Macroglial plasticity and the origins of reactive astroglia in experimental autoimmune encephalomyelitis.

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Public Summary:
Accumulations of hypertrophic, intensely glial fibrillary acidic protein-positive (GFAP(+)) astroglia, which also express immunoreactive nestin and vimentin, are prominent features of multiple sclerosis lesions. The issues of the cellular origin of hypertrophic GFAP(+)/vimentin(+)/nestin(+) "reactive" astroglia and also the plasticities and lineage relationships among three macroglial progenitor populations-oligodendrocyte progenitor cells (OPCs), astrocytes and ependymal cells-during multiple sclerosis and other CNS diseases remain controversial. We used genetic fate-mappings with a battery of inducible Cre drivers (Olig2-Cre-ER(T2), GFAP-Cre-ER(T2), FoxJ1-Cre-ER(T2) and Nestin-Cre-ER(T2)) to explore these issues in adult mice with myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis (EAE). The proliferative rate of spinal cord OPCs rose fivefold above control levels during EAE, and numbers of oligodendroglia increased as well, but astrogenesis from OPCs was rare. Spinal cord ependymal cells, previously reported to be multipotent, did not augment their low proliferative rate, nor give rise to astroglia or OPCs. Instead, the hypertrophic, vimentin(+)/nestin(+), reactive astroglia that accumulated in spinal cord in this multiple sclerosis model were derived by proliferation and phenotypic transformation of fibrous astroglia in white matter, and solely by phenotypic transformation of protoplasmic astroglia in gray matter. This comprehensive analysis of macroglial plasticity in EAE helps to clarify the origins of astrogliosis in CNS inflammatory demyelinative disorders.

Scientific Abstract:
Accumulations of hypertrophic, intensely glial fibrillary acidic protein-positive (GFAP(+)) astroglia, which also express immunoreactive nestin and vimentin, are prominent features of multiple sclerosis lesions. The issues of the cellular origin of hypertrophic GFAP(+)/vimentin(+)/nestin(+) "reactive" astroglia and also the plasticities and lineage relationships among three macroglial progenitor populations-oligodendrocyte progenitor cells (OPCs), astrocytes and ependymal cells-during multiple sclerosis and other CNS diseases remain controversial. We used genetic fate-mappings with a battery of inducible Cre drivers (Olig2-Cre-ER(T2), GFAP-Cre-ER(T2), FoxJ1-Cre-ER(T2) and Nestin-Cre-ER(T2)) to explore these issues in adult mice with myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis (EAE). The proliferative rate of spinal cord OPCs rose fivefold above control levels during EAE, and numbers of oligodendroglia increased as well, but astrogenesis from OPCs was rare. Spinal cord ependymal cells, previously reported to be multipotent, did not augment their low proliferative rate, nor give rise to astroglia or OPCs. Instead, the hypertrophic, vimentin(+)/nestin(+), reactive astroglia that accumulated in spinal cord in this multiple sclerosis model were derived by proliferation and phenotypic transformation of fibrous astroglia in white matter, and solely by phenotypic transformation of protoplasmic astroglia in gray matter. This comprehensive analysis of macroglial plasticity in EAE helps to clarify the origins of astrogliosis in CNS inflammatory demyelinative disorders.